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CORRESPONDENCE

Clinical predictors of COVID-19 severity and bleeding in the ACTIV-4B COVID-19 outpatient thrombosis prevention trial

To the Editor:

The ACTIV-4B trial randomized 657 symptomatic outpatients recently infected with SARS-CoV-2 to 45 days of treatment with aspirin 81 mg qd, apixaban 2.5 mg bid, apixaban 5 mg bid, or placebo. The primary analysis of the 558 participants who initiated treatment demonstrated that the majority do not require antithrombotic therapy--only 3 experienced an adjudicated endpoint of the primary composite outcome of all-cause mortality, symptomatic venous or arterial thromboembolism, myocardial infarction, stroke, and hospitalization for cardiovascular or pulmonary indication.[1] Although the trial answered the question of whether symptomatic stable COVID-19 outpatients should be given antithrombotic therapy, closing earlier than expected due to a low number of events, the predictive clinical characteristics of all randomized participants experiencing a positively adjudicated event encompassed in the definition of the primary composite outcome (3.6%) or a hemorrhagic event (5.3%) have not been described. This analysis identifies the relevant predictors of these events and bleeding events, with implications for the management of newly diagnosed outpatients.

Primary results of the ACTIV-4B trial and the study protocol, eligibility criteria, treatment allocation, methods for outcome assessment, and statistical analysis plan have been reported.[1] The trial primary endpoint was defined as the composite of symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischemic stroke, hospitalization for cardiovascular or pulmonary events, and all-cause mortality at 45 days. Although the primary analysis population was limited to randomized participants who took at least one dose of medication, all suspected primary endpoints occurring after randomization were adjudicated; this analysis includes all adjudicated primary endpoint events occurring in the complete set of randomized participants. The principal safety endpoints were ISTH defined major bleeding and clinically relevant non-major bleeding (CRNMB).[2] Bleeding events not meeting these definitions were classified as minor. Only suspected major or CRNMB bleeding events were adjudicated, however, all bleeding events were reviewed by investigators.

The cumulative incidence of each endpoint was estimated using Kaplan–Meier methods; differences by assigned treatment were tested with log rank statistics. Logistic regression was used for the occurrence of the primary endpoint, and Cox regression for time to the bleeding endpoint. Candidate explanatory variables included assigned treatment, all collected demographic and clinical history variables (age, sex, race/ethnicity, body mass index, history of smoking, past history of hypertension, diabetes, or venous thromboembolism), key laboratory variables (D-dimer, CRP, and creatinine clearance) and the number of days between SARS-CoV-2 test and randomization. Multivariable logistic and Cox regression models were created by including all variables individually associated with the outcome ($p < 0.10$) and applying backward stepwise regression to sequentially remove each factor with a p-value ≥0.10. The c-statistic and Harrell's concordance index quantified the discrimination of the final logistic and Cox regression models, respectively.

Among all 657 randomized participants, 26 suspected primary endpoints occurred during the 45-day period after randomization with 24 confirmed by adjudication (3.6%). The majority (21/24) occurred following randomization but before participants initiated assigned treatment, a median interval of 3 days [first quartile (Q1) - third quartile (Q3): 2–5 days].[1] All 24 confirmed events were hospitalizations for cardiovascular or pulmonary indications, with 23 admitted for progressive COVID-19 pneumonia, and 1 admitted for suspected myocardial infarction which was adjudicated as negative. Among the 23 patients hospitalized with progressive COVID-19 pneumonia, one non-fatal deep venous thromboembolism, one fatal pulmonary embolism, and one fatality due to respiratory failure also occurred during the 45-day treatment period. One death from prolonged respiratory failure occurring in the 30-day safety follow-up is not included in this analysis. In this population, the use of steroids and monoclonal antibodies, as well as vaccination rates, were low given the lack of availability of these treatments for outpatients during the enrollment period from September 2020 through June 2021.

Unadjusted risks of endpoint events, odds ratios, and hazards ratios for baseline variables are shown in Table 1. The cumulative incidence of the adjudicated primary endpoint in all randomized participants is shown in Figure 1A. All adjudicated primary COVID-related hospitalizations occurred within 10 days of randomization. As 21 of the 24 primary outcome events occurred prior to initiating treatment, the risk did not differ by assigned treatment (log rank $p = 0.78$). In the final multivariable model, male sex (AOR 2.99 [95% CI, 1.16, 7.73] $p = 0.024$), Black race (AOR 3.64 ([95% CI 1.10, 12.05] $p = 0.035$), Hispanic ethnicity (AOR 2.93 [95% CI 1.05, 8.20] $p = 0.040$), and elevated C-reactive protein (CRP) (AOR 1.36 [95% CI 1.01, 1.85]

TABLE 1 Observed risk for the adjudicated primary endpoint and all bleeding events endpoint among ACTIV-4B randomized participants ($N = 657$)

	Adjudicated primary endpoint		All bleeding events endpoint	
	Unadjusted risk n/N (%)	Unadjusted odds ratio (95% CI)	Unadjusted risk n/N (%)	Unadjusted hazard ratio (95% CI)
Age, per year	–	1.03 (0.98, 1.07)	–	0.99 (0.96, 1.03)
Age				
40 - ≤50 years	8 /260 (3.1%)	1.0	17/260 (6.5%)	1.0
> 50- ≤60 years	9 /260 (3.5%)	1.13 (0.43, 2.97)	9/260 (3.5%)	0.52 (0.23, 1.16)
> 60- ≤80 years	7/137 (5.1%)	1.70 (0.60, 4.78)	9/137 (6.6%)	1.01 (0.45, 2.26)
Sex				
Male	17/269 (6.3%)	3.67 (1.50, 8.98)	14/269 (5.2%)	0.98 (0.50, 1.92)
Female	7/388 (1.8%)	1.0	21/388 (5.4%)	1.0
Race/ethnicity				
Black non-hispanic	7/70 (10.0%)	6.38 (2.17, 18.81)	8/70 (11.4%)	2.29 (1.02, 5.18)
Hispanic	10/178 (5.6%)	3.42 (1.28. 9.13)	6/178 (3.4%)	0.66 (0.26, 1.62)
White non-hispanic	6/366 (1.6%)	1.0	19/366 (5.2%)	1.0
Other race/ethnicity	1/43 (2.3%)	1.0	2/43 (4.7%)	1.0
Time from SARS-CoV-2 test to randomization, per day	–	0.69 (0.59, 0.82)	–	0.93 (0.86, 1.01)
Time from SARS-CoV-2 test to randomization				
0–2 days	15/124 (12.1%)	1.0	14/124 (11.3%)	1.0
3–5 days	4/163 (2.5%)	0.18 (0.06, 0.57)	6/163 (3.7%)	0.30 (0.12, 0.78)
6–9 days	5/174 (2.9%)	0.10 (0.04, 0.28)	7/174 (4.0%)	0.33 (0.13, 0.81)
≥10 days	0/196 (0.0%)	(≥ 6, 3–5 vs. 0–2)	8/196 (4.1%)	0.33 (0.14, 0.79)
Body mass index, per 1 kg/m^2	–	1.07 (1.01, 1.14)	–	1.02 (0.97, 1.07)
Body mass index				
≤30 kg/m^2	9/297 (3.0%)	1.21 (0.49, 2.95)	17/297 (5.7%)	0.94 (0.47, 1.85)
>30 kg/m^2	11/303 (3.6%)	(>30 vs. ≤30)	16/303 (5.3%)	(>30 vs. ≤30)
Missing	4/57 (7.0%)		2/57 (3.5%)	
History of smoking				
Yes	5/131 (3.8%)	1.06 (0.39, 2.89)	9/131 (6.9%)	1.38 (0.65, 2.95)
No/missing	19/526 (3.6%)	1.0	26/526 (4.9%)	1.0
Hypertension				
Yes	9/232 (3.9%)	1.10 (0.48, 2.56)	15/232 (6.5%)	1.40 (0.72, 2.74)
No/missing	15/425 (3.5%)	1.0	20/425 (4.7%)	1.0
Diabetes				
Yes	6/120 (5.0%)	1.52 (0.59, 3.91)	9/120 (7.5%)	1.57 (0.73, 3.34)
No/missing	18/537 (3.4%)	1.0	26/537 (4.8%)	1.0
History of DVT or PE		––		––
Yes	0/19 (0.0%)		0/19 (0.0%)	
No/missing	24/638 (3.8%)		35/638 (5.5%)	
D-dimer, per 1 unit	–	1.15 (0.90, 1.47)	–	1.13 (0.93, 1.37)
D-dimer				
≤1.0 times ULN	10/387 (2.6%)		19/387 (4.9%)	
>1.0–≤2.0 times ULN	8/146 (5.5%)	1.85 (0.76, 4.51)	7/146 (4.8%)	1.13 (0.55, 2.34)
>2.0 times ULN	2/68 (2.9%)	(>1.0 vs. ≤1.0)	5/68 (7.4%)	(>1.0 vs. ≤1.0)
Missing	4/56 (7.1%)		4/56 (7.1%)	
Ln CRP, per 1 unit	–	1.81 (1.34, 2.44)	–	1.27 (1.03, 1.57)

TABLE 1 (Continued)

	Adjudicated primary endpoint		All bleeding events endpoint	
	Unadjusted risk n/N (%)	Unadjusted odds ratio (95% CI)	Unadjusted risk n/N (%)	Unadjusted hazard ratio (95% CI)
CRP				
≤2 mg/L	2 /193 (1.0%)		8/193 (4.2%)	
>2–≤4 mg/L	1/122 (0.8%)	6.77 (1.98, 23.11)	3/122 (2.5%)	2.31 (1.13, 4.71)
>4 mg/L	19/311 (6.1%)	(>4 vs. ≤4)	24/311 (7.7)	(>4 vs. ≤4)
Missing	2/31 (6.5%)		0/31 (0%)	
Ln creatinine clearance, per 1 unit	–	0.42 (0.13, 1.34)	–	1.35 (0.54, 3.37)
Creatinine clearance				
30–90 ml/min	7/149 (4.7%)	1.45 (0.59, 3.60)	5/149 (3.4%)	0.53 (0.21, 1.38)
>90 mL/min	16/487 (3.3%)	(30–90 vs. >90)	30/487 (6.2%)	(30–90 vs. >90)
Missing	1/21 (4.8%)		0/21 (0%)	
Assigned treatment group				
Aspirin	6/164 (3.7%)	0.74 (0.25, 2.18)	7/164 (4.3%)	2.33 (0.60, 9.00)
Apixaban 2.5	5/165 (3.0%)	0.61 (0.20, 1.90)	11/165 (6.7%)	3.74 (1.05, 13.42)
Apixaban 5.0	5/164 (3.1%)	0.61 (0.20, 1.92)	14/164 (8.5%)	4.82 (1.39, 16.77)
Placebo	8/164 (4.9%)	1.0	3/164 (1.8%)	1.0

Abbreviations: CRP, C-reactive protein; DVT, deep vein thrombosis; PE, pulmonary embolus.

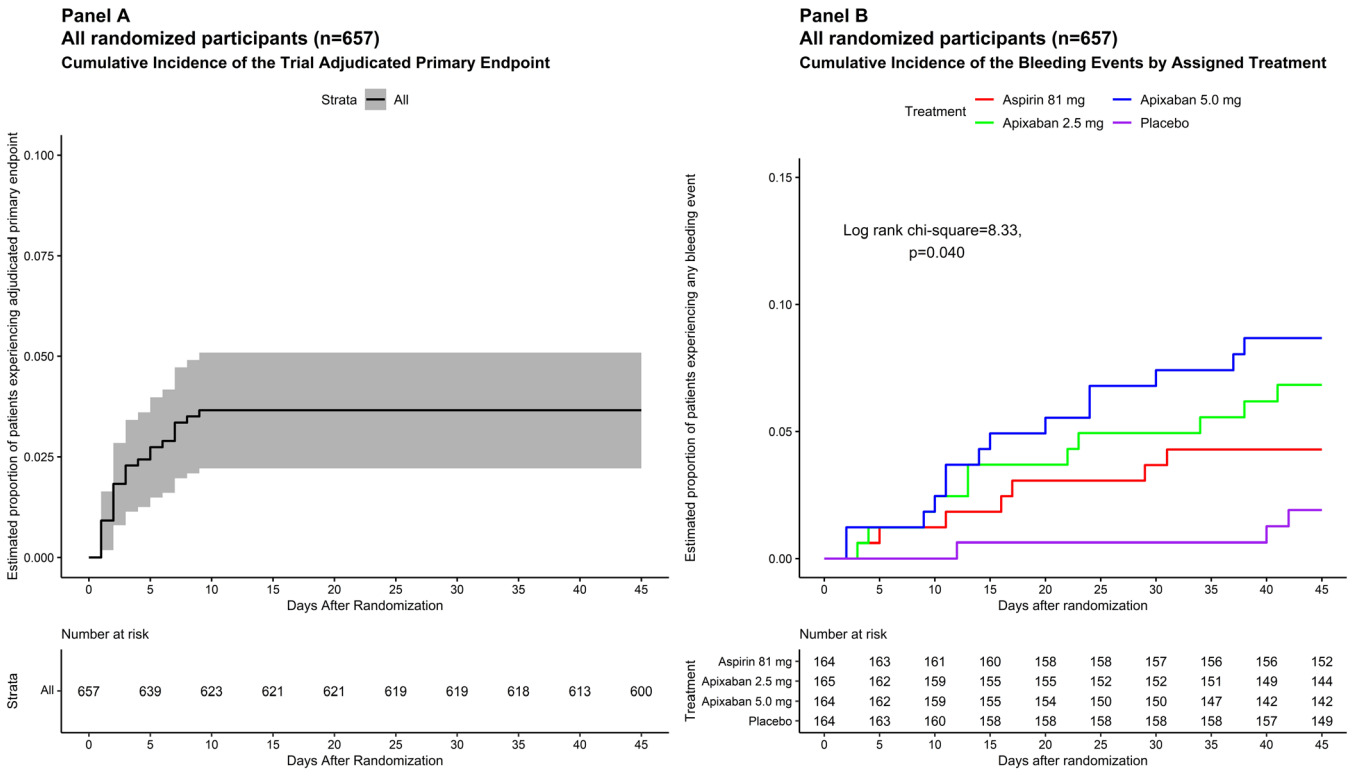

FIGURE 1 Cumulative incidence of the adjudicated primary trial endpoint (Panel A) and the cumulative incidence for any bleeding event (Panel B) stratified by assigned treatment group among randomized trial participants during the 45-day post-randomization follow-up period

$p = 0.046$) were independently associated with a greater risk of the primary endpoint (Table 2). Each day following a positive SARS-CoV-2 test result to randomization was associated with a 25% decreased risk of experiencing a primary endpoint (AOR 0.75 per day [95% CI 0.63, 0.88] $p = 0.001$). The c-statistic for the primary endpoint model was excellent: 0.874.

TABLE 2 Multivariable adjusted logistic regression model for adjudicated primary endpoint and multivariable Cox regression model for all bleeding event among ACTIV-4B randomized participants

All randomized participants, $N = 657$ number of primary endpoint events = 24	**Multivariable adjusted odds ratio (95% CI)**	***p*-value**
Male (versus Female)	2.99 (1.16, 7.73)	0.024
Black NH (versus White NH)	3.64 (1.10, 12.05)	0.035
Hispanic (versus White NH)	2.93 (1.05, 8.20)	0.040
Time from SARS-CoV-2 test to randomization, per day	0.75 (0.63, 0.88)	0.001
Ln CRP, per 1 unit	1.36 (1.01, 1.85)	0.046
Logistic regression c-statistic = 0.874		
All randomized participants, $N = 657$ number of bleeding events = 35	**Multivariable adjusted hazards ratio (95% CI)**	***p*-value**
Aspirin (versus Placebo)	2.51 (0.65, 9.70)	0.183
Apixaban 2.5 (versus Placebo)	3.95 (1.10, 14.15)	0.035
Apixaban 5.0 (versus Placebo)	4.87 (1.40, 16.93)	0.013
≤2 Days from SARS-CoV-2 test to randomization (versus >2 Days from test to randomization)	3.15 (1.60, 6.20)	0.001
Cox regression harrell's concordance statistic = 0.703		

Bleeding events occurred in 5.3% (35/657) of all randomized patients and in 7.6% (25/329) of those allocated to apixaban. Unlike the primary endpoint events which occurred soon after randomization, bleeding events accumulated steadily over the 45 days, with the cumulative incidence of bleeding events differing significantly by assigned treatment (log rank $p = 0.04$, Figure 1B). None were major; 6 were adjudicated as CRNMB, 3 in the apixaban 2.5 mg bid and 3 in the apixaban 5 mg bid groups. Factors significantly associated with an increased risk of bleeding included treatment with apixaban 2.5 mg bid (AHR 3.95 [95% CI 0.65, 9.70] $p = 0.035$) and apixaban 5 mg bid (AHR 4.87 [95% CI 1.40, 16.93] $p = 0.013$). Shorter time from positive SARS-CoV-2 test was associated with an increased risk of bleeding, such that ≤2 days from positive result to randomization was associated with AHR 3.15 (1.60, 6.20) $p = 0.001$. Race/ethnicity and biomarker values were not associated with the risk of bleeding, adjusting for treatment assignment and time (Table 2). Harrell's C-statistic indicated good discrimination (0.703).

While the primary results of the ACTIV-4B COVID-19 Outpatient Thrombosis Prevention Trial indicate that the majority of symptomatic but stable individuals infected with SARV-CoV-2 do not have a thrombotic risk high enough to justify prophylactic antithrombotic therapy, 3.6% of trial participants were hospitalized for progressive COVID-19 manifestations including three of whom died during trial follow-up. Recognition of the clinical predictors associated with these events is of clinical importance to identify those with COVID-19 likely to rapidly progress who might benefit from early aggressive intervention.

Observational data from electronic health records and health claims database analyses have identified older age, obesity, co-morbid cardiac or pulmonary disease, elevated CRP, male sex, and race/ethnicity, as risks for increased morbidity and mortality associated with COVID-19.[3–8] Updated CDC guidance (August 2021) lists conditions associated with higher risk for severe COVID-19; only obesity and comorbid medical conditions including cancer, heart disease, pulmonary disease, and liver disease are included in the highest tier "conditions with evidence" category.[9] The ACTIV-4B trial confirms in a randomized outpatient population that male sex, Black race, Hispanic ethnicity, and elevated CRP, are strongly predictive of hospitalization, as is shorter duration of time from positive SARS-CoV-2 test to randomization. Age, obesity, and D-Dimer level, associated with poor outcomes in observational studies, were not predictive in this sample. While D-dimer has been found to predict severity of COVID-19 in hospitalized patients,[10] the association with the primary endpoint was not significant in this analysis, possibly due to early or low level of infection as 90% of ACTIV-4B participants had minimal to no elevation in D-dimer at the time of enrollment; roughly 65% had a normal D-dimer and another 25% had only a minimal elevation between 1 and 2 times the upper limit of normal.[1] Time from positive SARS-CoV-2 test to events is also identified as an important predictor, as the risk for a primary endpoint event decreased significantly by 25% per day each day following a positive test result, again suggesting that early aggressive treatment with monoclonal antibodies, antivirals, or other treatments in the outpatient setting might benefit males, Blacks, those of Hispanic ethnicity, or those with elevated CRP. The monoclonal antibodies bamlanivimab-etesevimab, casirivimab-imdevimab, and sotrovimab with FDA emergency use authorization for use in high-risk outpatients do not explicitly include any of the risk factors identified in this study.[11] Some participants were hospitalized before initiating assigned treatment; It is not known whether starting antithrombotics at the time of positive SARS-CoV-2 test for those with the risk factors identified in ACTIV-4B would be of benefit or is achievable in an outpatient clinical trial.

As anticipated, the major predictors of bleeding were increasing anticoagulant dose. The shorter time period between positive SARS-CoV-2 test and randomization was also predictive of bleeding yet the biological basis for this is unclear as bleeding events included mild

hemoptysis but also menorrhagia and mild GI bleeds. Few randomized participants had renal function or platelet count values outside the normal range; median creatinine clearance was 114.1 (Q1-Q3: 91.2–143.6) and median platelet count 246.0 (Q1-Q3: 191.0–307.0), neither of which would affect bleeding risk. Bleeding is a second actionable factor in restricting antithrombotic therapy in this setting as the benefit–risk assessment favors no treatment in the majority of infected outpatients. Although the majority of bleeding events were minor, participants self-reported these events in open-ended survey questions. Early discontinuation of assigned treatment occurred in some, often stopped by participants themselves, or non-study affiliated care providers, prior to 45 days, after any bleeding was experienced.

The results of this analysis are limited by the low number of primary outcome events. Shifting demographic characteristics during the second wave of the pandemic when ACTIV-4B was enrolling compared to the onset of the pandemic, including younger age of infected patients and greater hospital bed availability, likely contributed to lower event rates than anticipated. SARS-CoV-2 variants such as delta and omicron were not present in large numbers of the population during the time the trial was conducted. These factors may reduce the generalizability of these results in the evolving landscape of the COVID-19 pandemic. Despite these limitations, knowledge of the predictors of poor outcomes identified in this randomized trial of stable COVID-19 outpatients has relevance for clinical practice, mechanistic causes of hospitalization, and future clinical trial design of COVID-19 infection in the outpatient setting.

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CONFLICT OF INTEREST

In addition to receiving research support from NIH to conduct this trial, Jean M Connors discloses personal fees for scientific advisory boards and consulting from Abbott, Anthos, Alnylam, Bristol Myers Squibb, Five Prime Therapeutics, Pfizer, Takeda, and research funding from CSL Behring; Paul M Ridker discloses that he has received research grant support and served as a consultant to Bristol-Myers Squibb and Pfizer for work unrelated to this project, as well as unrelated consulting from Corvidia, Novartis, Flame, Agepha, Inflazome, AstraZeneca, Jannsen, Civi Biopharm, SOCAR, Novo Nordisk, Uptton, and Omeicos, and Boehringer-Ingelheim; Maria M Brooks discloses that she serves as a DSMB member for Cerus Corporation; the remaining authors do not declare any conflicts of interest related to the ACTIV-4B project or to diagnostics or therapeutics related to COVID-19.

AUTHOR CONTRIBUTIONS

Jean M Connors, Maria M Brooks, Frank C Sciurba, and Paul M Ridker designed the study. Maria M Brooks, and Zhuxuan Fu analyzed the data. Jean M Connors drafted the manuscript. All authors revised the manuscript for intellectual content, approved the final manuscript, and agreed to submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from NIH. Restrictions apply to the availability of these data, which were used under license for this study. Data are available after 01/01/2023with the permission of NIH.

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